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Ethylzincation of Monosubstituted Alkenes Catalyzed by EtMgBr−Cl_2ZrCp_2 and Palladium-Catalyzed Cross Coupling of the Resultant Diisoalkylzinc Derivatives

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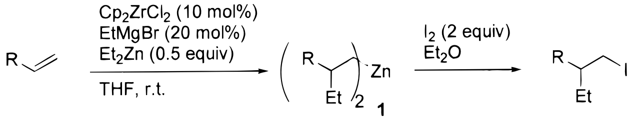
Summary: The reaction of monosubstituted alkenes with 0.5 molar equiv of Et_2Zn in the presence of a catalyst generated in situ by treatment of Cl_2ZrCp_2 with 2 molar equiv of EtMgBr produces regioselectively the corresponding diisoalkylzincs **1***, generally in high yields. Their direct cross coupling with a variety of organic halides in the same reaction vessel can be achieved in good yields with a catalytic amount of a palladium complex.*

Herein reported is a novel ethylzincation of monosubstituted alkenes with diethylzinc and a catalyst generated in situ by the treatment of Cl_2ZrCp_2 with 2 molar equiv of EtMgBr. The reaction produces regioselectively diisoalkylzincs **1**, generally in high yields (Table 1). Their cross coupling with a variety of organic halides can be achieved in good yields with catalytic amounts of palladium complexes. Although the allylzincation of alkenes has been known for many decades and is well-documented,[2] this ethylzincation appears to be novel. In contrast with the Zr-catalyzed carboalumination of 1-alkenes,[3] all carbon groups bonded to Zn undergo carbometalation. The carbozincation reaction is also cleaner and higher yielding than the Dzhemilev carbomagnesation.[4] Unlike the latter, which generally requires an excess of an ethylmagnesium derivative, all Et groups are incorporated in the products in high yields. Furthermore, the isoalkyl−Zn bonds readily undergo Pd-catalyzed cross coupling with various organyl halides (Table 2). The corresponding reactions of isoalkylmetals containing Mg are much more sluggish and lower yielding, and isoalkylalanes fail to undergo Pd-catalyzed cross coupling.

Table 1. Ethylzincation of Monosubstituted Alkenes with Diethylzinc and EtMgBr−Cl_2ZrCp_2, in Catalytic Amounts



R of $RCH{=}CH_2$	reacn time, h[a]	product yield $RCH(Et)CH_2I$, %[b]	unreacted starting alkene, %[b]
n-octyl	4	95 (90)	5
cyclohexyl	4	74 (68)	20
benzyl	4	84 (80)	14
phenyl	12	58 (45)	10[c]

[a] All reactions were conducted at room temperature in THF. [b] Yields were calculated by GC using mesitylene as an internal standard. Figures in parentheses are isolated yields (isolated by distillation). [c] High-molecular-weight byproducts were observed.

The intramolecular nickel-catalyzed carbozincation of alkynes[5a] and the intramolecular palladium-catalyzed carbozincation of alkenes[5b] are very effective.[6] However, the corresponding Ni-catalyzed intermolecular carbozincation of alkynes is generally sluggish and is of limited scope.[7c] Although carbozincation of alkynes can be achieved rather cleanly using catalytic amounts of zirconocene diiodide,[7a,b] its scope also remains limited. We therefore sought alternative metal-catalyzed procedures for carbozincation of alkenes and have found that the reaction of monosubstituted alkenes with diethylzinc can indeed be catalyzed by zirconium. Without a catalyst, no reaction was observed. Furthermore, it was necessary to treat zirconocene dichloride with 2 molar equiv of EtMgBr before the reaction. Specifically, the best results were obtained for 1-decene with the following procedure. A solution of EtMgBr (20 mol %) in Et_2O was added dropwise at −78 °C to a solution of zirconocene dichloride (10 mol %) in THF. After 5 min, 1 molar equiv of alkene was added. The reaction mixture was then brought to 23 °C over 20 min. Finally, a solution of 0.5 molar equiv of a 1 M solution of Et_2Zn in hexanes was added at 23 °C, and the reaction mixture was stirred at this temperature. Quenching with iodine in Et_2O or THF afforded 1-iodo-2-ethyldecane in 95% yield. Using this procedure, the scope of the ethylzincation was examined. As the results summarized in Table 1 indicate, the reaction appears to be reasonably general with respect to the R group of monosubstituted

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(1) Purdue Research Foundation Graduate Research Fellow (1999−2000).

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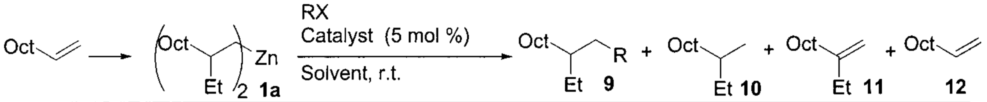
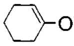
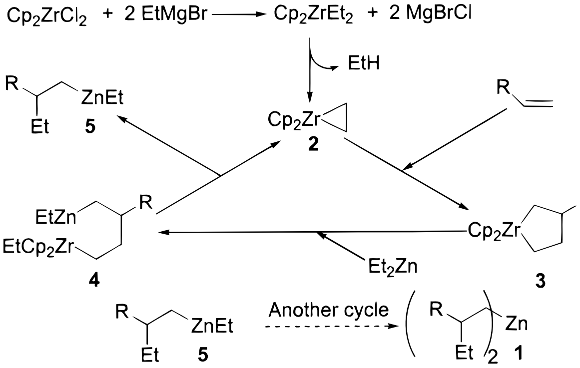
Table 2. Pd-Catalyzed Cross Coupling of the Diisoalkylzinc Generated by Ethylzincation of 1-Decene with Various Organic Halides



RX	catalyst	solvent	time, h[b]	**9** (%)[a]	**10** and **11**(%)[a]	**12** (%)[a]
PhI	$Cl_2Pd(dppp)$	DMF	12	80(60)	10 and 7	0
PhI	$Cl_2Pd(dppp)$	THF	12	0	90 (combined)	0
PhI	$Cl_2Pd(dppf)$	DMF	12	75	20 (combined)	0
PhI	$Cl_2Pd(dppf)$	THF	12	45	10 and 40	0
PhI	$Cl_2Pd(dppb)$	DMF	12	80	10 and 10	0
PhI	$Cl_2Pd(P(TFP)_3)_2$	THF	12	30	30 (combined)	10
PhI	$Cl_2Pd(PPh_3)_2$	DMF	12	50	45 (combined)	0
PhI	$Pd(DBA)_2$+2TFP	DMF	12	Traces	90 (combined)	0
PhI	$Pd(PPh_3)_4$	DMF	12	0	85 (combined)	0
PhI	$Cl_2Pd(dppp)$	DMF	16[c]	70	30 (combined)	0
PhI	$Cl_2Pd(dppp)$	DMF	16[d]	80	20 (combined)	0
$2\text{-}MeC_6H_4I$	$Cl_2Pd(dppp)$	DMF	20	65	10 and 15	5
$CH_2{=}CHBr$	$Cl_2Pd(dppp)$	DMF	12	76 (65)	9 and 9	7
-OTf[15]	$Cl_2Pd(dppp)$	DMF	60	10	80 (combined)	0
$CH_2{=}CHCH_2Br$	$Cl_2Pd(dppp)$	DMF	12	60 (45)	15 and 15	8
$PhCH_2Cl$	$Cl_2Pd(dppp)$	DMF	60	40	10 and 45	0
$HC{\equiv}CCH_2Br$	$Cl_2Pd(dppp)$	DMF	60	45	10 and 40	0
PhCOCl	$Cl_2Pd(dppp)$	DMF	20	75 (70)	5 and 15	0

[a] All yields were calculated by GC using mesitylene as an internal standard. Figures in parentheses are isolated yields (isolated by distillation). [b] All reactions were carried using 4 molar equiv of RX, unless otherwise noted. [c] 1 molar equiv of PhI was used. [d] 2 molar equiv of PhI was used.

Scheme 1



alkenes. It should be mentioned, however, that allyl benzyl ether and allyl phenyl ether do not yield detectable amounts of ethylzincated products.

In light of the previous mechanistic studies on carboalumination[8] and carbomagnesation,[4b] the mechanism of this carbozincation can be thought to proceed as depicted in Scheme 1. Treating zirconocene dichloride with 2 molar equiv of EtMgBr has been shown to generate diethylzirconocene, which undergoes β-hydrogen abstraction to give the zirconocene–ethylene complex **2**.[9] This zirconocene–ethylene complex thus prepared in situ can react with 1 molar equiv of alkenes to give regioselectively β-substituted zirconacyclopentanes **3** in high yields.[10] In the presence of 1 molar equiv of Et_2Zn, transmetalation evidently occurs regioselectively to give the bimetallic intermediate **4**. The observed regioselectivity may be due to the relief of steric hindrance to a greater extent, since the zirconocene unit ends up at the less crowded site. The dialkylzirconocene intermediate **4** would then undergo a chemoselective β-hydrogen abstraction involving selective abstraction of a β-H atom of the Et group[9] to give **5** and regenerate the zirconocene–ethylene complex. A similar reaction of **5** involving the second ethyl–zinc bond will give ultimately the diorganylzinc **1**.[11] To support this mechanism, the following experiments were conducted. The ethylene–zirconocene complex **6** stabilized by 1 molar equiv of methyldiphenylphosphine was generated according to a reported procedure[12] and used in catalytic quantities in the reaction of 1-decene with Et_2Zn (Scheme 2, eq a). Ethylzincation took place and afforded the expected 2-ethyldecane in 60% yield after 12 h. Similarly, the use of the β-substituted zirconacyclopentane **7** generated from zirconocene dichloride and

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(8) (a) Van Horn, D. E.; Negishi, E. *J. Am. Chem. Soc.* **1978**, *100*, 2252. (b) Yoshida, T.; Negishi, E. *J. Am. Chem. Soc.* **1981**, *103*, 4985. (c) Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639.

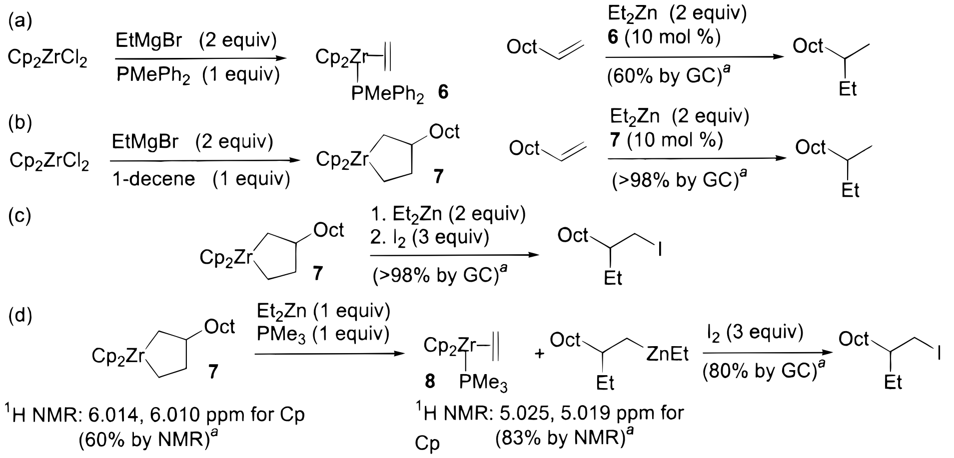
(9) Negishi, E.; Nguyen, T.; Maye, J. P.; Choueiri, D.; Suzuki, N.; Takahashi, T. *Chem. Lett.* **1992**, *114*, 10091.

(10) (a) Swanson, D. R.; Rousset, C. J.; Negishi, E.; Takahashi, T.; Seki, T.; Saburi, M.; Uchida, Y. *J. Org. Chem.* **1989**, *54*, 3521. (b) Negishi, E.; Miller, S. R. *J. Org. Chem.* **1989**, *54*, 601. (c) Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 6266.

(11) With 1-decene as a substrate, in hexanes and with higher loads of Et_2Zn (1–2 molar equiv with respect to the alkene), the formation of 1-iodo-2-(2-iodoethyl)decane after quenching with iodine was observed, suggesting that a second transmetalation had occurred before the β-hydrogen abstraction took place.

(12) Takahashi, T.; Suzuki, N.; Hasegawa, M.; Nitto, Y.; Aoyagi, K. I.; Saburi, M. *Chem. Lett.* **1992**, 331.

Scheme 2



^{a} All yields were calculated using mesitylene as an internal standard.

1-decene[10] in place of **6** afforded the expected 2-ethyldecane in >98% yield after 4 h (Scheme 2, eq b). The β-substituted zirconacyclopentane **7** was also treated with 2 molar equiv of Et_2Zn. Iodination gave 1-iodo-2-ethyldecane in more than 98% yield (Scheme 2, eq c). The ^{1}H NMR spectrum of the β-substituted zirconacyclopentane **7** showed two Cp signals at 6.010 and 6.014 ppm. After treatment with 1 molar equiv each of Et_2Zn and PMe_3, the ^{1}H NMR spectrum of the reaction mixture **8** showed two Cp signals at 5.019 and 5.025 ppm (Scheme 2, eq d).

The Pd-catalyzed cross coupling of the diisoalkylzincs **1a** generated by ethylzincation of 1-decene can be achieved in good yields with a variety of electrophiles. The optimal conditions were sought for the case of cross-coupling with phenyl iodide, and the results are summarized in Table 2. The use of $Pd(PPh_3)_4$ as a catalyst does not yield any cross-coupling product in detectable amounts. Derivatives of $PdCl_2$ appear to be much more preferable. The major byproducts are 2-ethyldecane due to the unreacted organozinc reagent and 2-ethyl-1-decene due to dehydropalladation.[13] The latter can be considerably reduced by the use of chelating ligands on palladium such as dppf, dppp, and dppb. Indeed, the dehydropalladation occurs after the isoalkylpalladium intermediate is formed by transmetalation from the isoalkylzinc. On the other hand, $Cl_2Pd(TFP)_2$, where TFP is tris(2-furyl)phosphine, $Cl_2Pd(PPh_3)_2$, and $Pd(dba)_2$ + 2 TFP give poor yields of cross-coupling products in either THF or DMF. With $Cl_2Pd(dppf)$, $Cl_2Pd(dppp)$, and $Cl_2Pd(dppb)$, high yields of cross coupling products are obtained in DMF. THF seems to be detrimental to the cross coupling, and it has to be removed by evaporation under vacuum before cross coupling. It is noteworthy that the cross-coupling reactions of the carbomagnesation and carboalumination products of 1-decene with phenyl iodide using $Cl_2Pd(dppp)$ or $Cl_2Pd(dppf)$ as a catalyst were unsuccessful. Carbomagnesation of 1-decene, addition of $ZnBr_2$ or $ZnCl_2$, evaporation of the solvents, and cross coupling with phenyl iodide under the conditions used in Table 2 did provide the desired cross-coupled product in moderate yield. However, the carbozincation reaction itself is significantly higher yielding and cleaner than the corresponding carbomagnesation reaction, as is the carbozincation−cross coupling tandem process. Using 5 mol % of $Cl_2Pd(dppp)$ in DMF at 23 °C, the scope of the Pd-catalyzed cross coupling was examined. As the results summarized in Table 2 indicate, a variety of electrophiles can be cross-coupled satisfactorily. However, 2-ethyl-1-decene is the major product when the cross coupling is very slow.[14]

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Supporting Information Available: Text giving details of the synthesis and characterization data for the compounds discussed in the paper and figures giving NMR spectra of these compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] (a) When 1 or 2 molar equiv of Et_2Zn was used to perform the ethylzincation, the organozinc generated was an (ethyl)(isoalkyl)zinc species and byproducts from the cross coupling between the ethyl moiety and the electrophile were observed but remained minor. (b) Traces of biphenyl byproduct were observed.

[14] When a large excess of electrophile was used, homocoupling of the electrophile was observed in fair amount (with 4 molar equiv of PhI, about 40% of PhPh was formed).

[15] 1-Cyclohexenyl triflate was generated according to a reported procedure: (a) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. (b) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.